May 23 1953

Dear Phil:

Your letters of the 15th and 20th came in yesterday and today respectively. I cannot imagine why the former should have been delayed.

Naturally, I am delighted to get the manuscript back so soon. I will work it over again at the earliest opportunity, probably Monday. Unfortunately for the present problem, I have been extremely distracted all this last week by visitors (E.S. Anderson and L.S. Baron), and I have not even had time to digest your letters. I will write you again in two or three days.

I agree on a conservative approach in this paper, to encompass whatever differences there may be. I hope that the paper already does this for the most part.

I am very sorry not to have been more methodical in summarizing the cultures that have been exchanged. I was just about to set up such a list for you, when I got your letter.

Will the following procedure be acceptable to you? I will go over the ms. with your revises, and exercise my own judgment about them. Unless there seems to be a vital issue, I will go ahead and have several copies mimeographed, and will send you 6 (six)--please let me know if more will be necessary. I will also send 2 to the Journal of Immunology. I am sure we will have an opportunity for any last minute changes when the paper is returned from the reviewer. I am rather indifferent, myself, about the positioning of adverbs modifying perfect verbs, and will follow your line except where the alternative sounds definitely better. Anderson tells me that English practice (cf. Fowler) is much less rigid than that prescribed by your "editor"! I asked him to read the paper, which he claims to have enjoyed. He particularly thought the detail on the method of melting off agar tubes should be left in (with slight modification of phrase) unless it is explicitly given elsewhere. Anyone not aware of that small trick will make a mess of it (as I have done in the past), and this may have encouraged the other modifications.

I believe that SW-435 was left after my visit in February. Bailey may have it.

SW-1031 is SW-1026[= SW623 (SW-666x-TM)i:— —x N97 ph 1,2:] [redacted]— sendai a:- and is a:b.

The java N97 story finally begins to make sense. Typical paratyphi B is H_1^b $H_2^{1,2}$, that is, it has a b factor homologous with typical first phases, and a 1,2 homologous with typical second phases. N97 seems to be H_1^b $H_1^{1,2}$, with a very sluggish phase variation. That is, N97 carries two factors both homologous with typical first phases. This accounts for the ability to transduce other first phases into N97, to obtain such monstrosities as a:b and b:i (H_1^a H_1^b ($H_1^{1,2}$)

This can be carried one step further, as has just been completed:

S. altendorf c:1,7 —x SW-1031 a:b gave c:b (SW-1052)

—x a:b gave c:a (SW-1053).

The latter is the most instructive. Two typical H_1 factors, c and a, have been transduced to $H_1^{b}\ H_1^{1,2}$ to give $H_1^{c}H_1^{a}$. This kind of doubling of homologues in a single set is not unknown by any means in the genetics of other organisms, so called "duplication". It is the standard explanation of how a limited number of genetic factors can begin to diversify and become more complex. Please don't fuss over this if I haven't made it clear. There is one more experiment that should finish it up: I have transduced H_2^{enx} from S. abony to SW-1053. If this gives a triphasic a:c:enx, the idea of a duplication of the H_1 loci will be nicely supported. As soon as this result comes in, I'll try to write up the whole story in a coherent way so that I can understand it myself. I didn't put this in before, N97 presumably is $H_1^{b}\ H_1^{1,2}\ H_2^{-}$ since an H_2 factor can be brought in. The very sluggish phase variation between b and 1,2 is the chief technical difficulty.

N25 would presumably be a similar story except that b → 1,2 and reverse occurs with an even lower frequency precluding detailed study.

I meant to keep this a short preliminary letter. I did want to ask if you had seen reprints of Iseki's paper on the newington E2 : anatum E1 variation story.(Proc. Japan Acad. 1953). The gist of his story, as best I can understand it, is that E2 carries a phage which, by simply infecting E1, converts this to E2. Conversely, treatment of E2 with serum (adsorbed with boiled E1) results in the loss of this phage, and the conversion to E1. [Do you recall our discussions of this problem?] If you happen still to have the old intertransformed strains of ~~cambridge and~~ newington and anatum, it should be simple enough to check this claim [which I can't say I'm entirely convinced of], by looking for the phage. On this notion, the change from E1 to E2 would involve a contamination of the serum with phage, in your 1947 experiments. Using serums absorbed with boiled cells he was able to get E1 from E2, but unlike your result with unboiled cells, not E2 from E1.

If you'd gotten his reprints, I hope you were able to understand it better than I did. I may have gotten it all wrong.

So long for now,

Joshua Lederberg

P.S. That SW-1041 (S. gallinarum —x) result was very interesting. It will be curious to see whether all the others behave alike. The two gallinarum strains that didn't work probably gave only low phage titers, and have to be worked over some more. Are there any special ecological or biochemical types of S. enteritidis to which S. gallinarum can be particularly related? I will have to do some nutritional studies along this line, as S. gallinarum is characteristically dependent on thiamine.

JL